Hyponatremia

Physicians may face difficulties treating patients who have hyponatremia. The risks of rapid correction, such as pontine myelinosis, are well known. Also, many and sometimes complex factors influence the serum sodium concentration.

A 72-year-old woman from a nursing home presents to the emergency department with a change in her mental state over the past few hours. She has a medical history of coronary artery disease and hypertension. Her medications include hydrochlorothiazide, 25 mg a day, and aspirin, 81 mg a day. On physical examination, she has decreased skin turgor, orthostatic hypotension, and disorientation to time, place, and person without focal neurologic deficits. Initial laboratory tests show a serum sodium level of 110 mmol/L; blood urea nitrogen, 23.2 mmol/L (65 mg/dL); creatinine, 318 µmol/L (3.6 mg/dL); triglycerides, 2.75 mmol/L (244 mg/dL); and plasma osmolality, 278 mmol/kg of water (278 mOsm/kg of water). Other laboratory findings are a bicarbonate value of 29 mmol/L; hematocrit, 0.35 (35%); potassium, 4.0 mmol/L; uric acid, 0.42 mmol/L (7.0 mg/dL); urine osmolality, 450 mmol/kg of water; and urine specific gravity, 1.019. Her serum sodium level 2 months before admission was 135 mmol/L, and her urine output was 400 mL a day. She is admitted to the hospital, and a regimen of intravenous isotonic sodium chloride solution is started at a rate of 84 mL per hour in the first 24 hours.

Summary points

- Hyponatremia is a common clinical disorder that requires careful management
- Older people are predisposed to hyponatremia, and the incidence is highest in this age group
- When hyponatremia is accompanied by central nervous system manifestations (hyponatremic encephalopathy), substantial morbidity is seen, whereas asymptomatic hyponatremia is usually benign
- Symptomatic hyponatremia requires treatment, usually by hypertonic sodium chloride infusion. Correction should be limited to about 25 mmol/L during the initial 24 to 48 hours.

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METHODS

Searching the literature

Once we had formulated the specific clinical questions, we searched the OVID database using the search term *hyponatremia.* We limited the search to the subheadings *diagnosis, complications,* and *therapy* and the publication years of 1991 through 2001. The search elicited 126 articles, of which 17 were relevant and in peer-reviewed journals.

PERTINENT QUESTIONS

How common is hyponatremia?

Hyponatremia is the most frequent electrolyte abnormality seen in general hospital patients, with an incidence of about 1%. Symptomatic hyponatremia is equally common in men and women, but children and menstruating women are more vulnerable to hyponatremic brain damage.[1]

What are the symptoms of hyponatremia?

The symptoms of hyponatremia are primarily neurologic and are related both to the severity and in particular to the rapidity of onset of the change in the plasma sodium concentration. Patients also have symptoms related to concurrent volume depletion and to possible underlying neurologic disorders that predispose to the electrolyte abnormality.[2-4] The presence of symptoms and the duration of the hyponatremia guide the treatment strategy.[5]

Nausea and malaise are the earliest findings and may be seen when the plasma sodium concentration falls below 125 to 130 mmol/L. This may be followed by headache, lethargy, obtundation, and eventually seizure, coma, and respiratory arrest if the plasma sodium concentration falls below 115 to 120 mmol/L.[6,7] In one study of 184 patients with a plasma sodium concentration of 120 mmol/L or less, 11% presented in coma.[7]

Hyponatremic encephalopathy is often reversible. The degree of cerebral edema and, therefore, the likelihood of neurologic symptoms is much less with chronic than with acute hyponatremia.[8] When patients with chronic hyponatremia have symptoms, the plasma sodium concentration is generally below 110 mmol/L, and there has usually been an acute exacerbation of the hyponatremia.

What are the common causes of hyponatremia?

In almost all patients, hyponatremia results from the intake (either oral or intravenous) and subsequent retention of water (see box 1).[1] A water load will, in healthy persons, be rapidly excreted; the dilutional fall in plasma osmolality

Box 1 Major causes of hyponatremia

Disorders in which ADH levels are elevated

- Effective circulating volume depletion
- True volume depletion—vomiting, diarrhea, bleeding, urinary loss
- Congestive heart failure and cirrhosis
- Thiazide diuretics
- Syndrome of inappropriate ADH secretion
- Hormonal changes: adrenal insufficiency, hypothyroidism, and pregnancy

Disorders in which ADH may be appropriately suppressed

- Advanced renal failure
- Primary polydipsia
- Beer drinkers' potomania

Pseudohyponatremia

- High plasma osmolality: hyperglycemia or mannitol
- Normal plasma osmolality: hyperlipidemia, glycine solutions, and hyperproteinemia

suppresses the release of antidiuretic hormone (ADH), thereby allowing the excretion of dilute urine. The maximum rate of water excretion on a regular diet is more than 10 L per day, thereby providing an enormous range of protection against the development of hyponatremia.

Many commonly used drugs can cause hyponatremia, either by dilution (such as antipsychotic drugs, carbamazepine, cyclophosphamide, desmopressin acetate, vincristine sulfate, and octreotide acetate) or by salt wasting (such as enemas).

How is the fluid status of a patient assessed?

Hyponatremia is defined as a decrease in the serum sodium concentration to a level below 136 mmol/L. It can be associated with low, normal, or high tonicity. Effective osmolality or tonicity refers to the contribution to the osmolality of solutes (eg, sodium and glucose) that cannot move across the cell membranes, thereby inducing transcellular shifts in water. Dilutional hyponatremia, by far the most common cause of hyponatremia, is caused by water retention. If water intake exceeds the capacity of the kidneys to excrete water, body solutes dilute, causing hypoosmolality and hypotonicity.

An accurate history and physical examination can help to determine whether the patient has hypovolemia, euvolemia, or hypervolemia and the cause of volume depletion. Hypovolemia refers to any condition in which the extracellular fluid volume is reduced. When severe, it leads to a clinically apparent reduction in tissue perfusion. It can be produced by salt and water loss or by water loss alone (ie, dehydration). Salt and water loss comes primarily from the extracellular fluid, whereas pure water loss comes from the total body water, only about 40% of which is extracellular. Thus, for dehydration to produce the same degree of extracellular volume depletion as salt and water loss, 2.5 times as much fluid would have to be lost.

A decrease in the interstitial volume can be detected by examining the skin and mucous membranes. If the skin of the arm, calf, or thigh is pinched in healthy subjects, it will immediately return to its normally flat state when the pinch is released. This elastic property, called turgor, is lost when there is a loss in the interstitial fluid. A decrease in the plasma volume can lead to variations in the systemic blood pressure and the venous pressure in the jugular veins. The arterial blood pressure changes from normal to low in the upright position and then, with progressive volume depletion, to persistently low despite posture.

What laboratory tests are most useful in finding the cause of hyponatremia?

After a thorough history and physical examination, essential laboratory tests include the plasma osmolality, the urine osmolality, and the urine sodium concentration.[2] Baseline thyroid-stimulating hormone, hemoglobin, albumin, potassium, and bicarbonate levels can also be valuable, for reasons discussed later.

The plasma osmolality is reduced in most hyponatremic patients because it is primarily determined by the plasma sodium concentration and accompanying anions. In some patients, however, the plasma osmolality is either normal or elevated.[2,9]

The normal response to hyponatremia is to completely suppress ADH secretion, resulting in the excretion of a maximally dilute urine with an osmolality below 100 mmol/kg of water and a specific gravity of 1.003 or lower. Higher values indicate an inability to normally excrete free water that is generally due to the continued secretion of ADH. Most hyponatremic patients are unable to produce dilute urine, and their urine osmolality may be 300 mmol/kg of water or even greater.

In those patients with hyponatremia and a low plasma osmolality, the urine osmolality can be used to distinguish between impaired water excretion and primary polydipsia, in which water excretion is normal but intake is so high that it exceeds excretory capacity. In patients with impaired water excretion due to hypovolemia, the urine osmolality often exceeds 450 mmol/kg of water.

In the absence of adrenal insufficiency or hypothyroidism, the two major causes of hyponatremia with hypoosmolality and inappropriately concentrated urine are volume depletion and the syndrome of inappropriate ADH secretion (SIADH). These disorders can usually be distinguished by measuring the urine sodium concentration,

which is typically below 25 mmol/L with volume depletion and above 40 mmol/L in patients with SIADH.[10] The initial water retention and volume expansion in patients with SIADH leads to another frequent finding that is the opposite of that typically seen with volume depletion: hypouricemia due to increased uric acid excretion in the urine.[11]

Either hypokalemia or hyperkalemia can occur in hypovolemic patients. The effect of fluid loss on the acid-base balance also varies; either metabolic alkalosis or acidosis can occur. Because red blood cells and albumin are essentially limited to vascular space, a reduction in the plasma volume tends to elevate both the hematocrit and the plasma albumin concentration.

In acute renal failure, the fractional excretion of sodium is a more accurate assessment of volume status than the urine sodium concentration (see box 2). A value of less than 1% in patients with acute renal failure suggests effective volume depletion. But the fractional excretion of sodium is more difficult to evaluate in patients with a normal glomerular filtration rate.

Box 2 Fractional excretion of sodium

$$\text{Fractional Excretion of Sodium} = \frac{\text{Urine Sodium Concentration} \div \text{Plasma Sodium Concentration}}{\text{Urine Creatinine Concentration} \div \text{Plasma Creatinine Concentration}} \times 100\%$$

How fast should the sodium be replaced in patients with symptomatic hyponatremia?

When considering the treatment of hyponatremic patients, four issues must be addressed: the risk of osmotic demyelination, the appropriate rate of correction to minimize this risk, the optimal method of raising the plasma sodium concentration, and estimation of the sodium deficit if sodium is to be given.

The adaptation that returns the brain volume toward normal in patients with chronic hyponatremia protects against the development of cerebral edema but also creates a possible problem for therapy. In patients with acute hyponatremia, an overly rapid increase in the plasma sodium concentration can lead to osmotic demyelination syndrome.[2,8,12] The changes can lead to possibly severe neurologic symptoms that are delayed for 2 to 6 days after correction and that may be irreversible.[12-14]

Based on a retrospective analysis of 64 patients, Sterns found that neurologic complications tend to occur if the rate of correction exceeds 0.6 mmol/L per hour. Of 62 of the 64 patients who were treated, 5 died (for a mortality of 8%). He concluded that most of the observed neurologic complications were not caused by the hyponatremia per se but were related to a rate of correction of the serum sodium concentration exceeding 0.55 mmol/L per hour.[15] On the other hand, other reviewers have indicated that the magnitude rather than the rate of correction is responsible for the development of neurologic complications.[15,16] In acute symptomatic hyponatremia that develops within 48 hours, treatment should be prompt because the risk of cerebral edema far exceeds the risk of osmotic demyelination.

After weighing the available evidence and the all-too-real risk of overshooting the mark, we recommend a targeted rate of correction that does not exceed 8 mmol/L on any day of treatment. Should severe symptoms not respond to correction to the specified target, this limit may be cautiously exceeded because the imminent risks of hypotonicity override the potential risk of osmotic demyelination.[17] The aim should be to raise the serum sodium concentration by 2 mmol/L per hour until symptoms have resolved.[18] Complete correction is unnecessary, although no risks are involved in restoring plasma sodium to normal levels.

If hyponatremia has been present for longer than 48 hours or the duration is unknown, as in the case of our patient, correction should be handled carefully.[5] In the treatment of hyponatremia, it is currently recommended that the plasma sodium concentration in asymptomatic patients should be elevated at a maximum rate of 10 to 12 mmol/L during the first 24 hours and 18 mmol/L over the first 48 hours.[8,12] Even at this rate, however, neurologic symptoms can develop.[15,19]

It is probably wise, therefore, to correct the hyponatremia at less than the maximum rate in asymptomatic patients. This can be accomplished by fluid restriction. To be effective, fluids need to be restricted to less than free water loss (free water loss is equal to urine output plus the water loss through sweating and stool).[18,20]

Vasopressin antagonists will soon become available. Preliminary experience has shown that they are effective in causing sustained diuresis and in correcting hyponatremia.[21]

How to calculate the sodium deficit

When an isotonic sodium chloride solution is given to treat hyponatremia, the quantity of sodium chloride required to achieve the desired elevation in the plasma sodium concentration can be estimated by multiplying the plasma sodium deficit per liter with the total body water, which represents the osmotic space of distribution of the plasma sodium concentration. Normal values for the total body water are 0.5 and 0.6 times the lean body weight (in kilograms) in women and men, respectively.

The initial aim in our patient (who weighed 60 kg [132 lb]) was to raise the plasma sodium concentration from 110 to 120 mmol/L.[2]

- Plasma sodium deficit per liter: 120 − 110 = 10 mmol
- Total body water: 0.5 × 60 = 30
- Sodium deficit for initial therapy = plasma sodium deficit per liter × total body water: 10 × 30 = 300 mmol

Thus, 600 mL of hypertonic sodium chloride (which contains roughly 1 mmol of sodium per 2 mL) should be given over 24 hours at a rate of 25 mL an hour; or 2,000 mL of isotonic sodium choride (which contains 1.5 mmol of sodium per 100 mL) should be given over 24 hours at a rate of about 84 mL an hour. This regimen should raise the plasma sodium concentration at the desired rate of 10 mmol/L during the first day.

The plasma sodium concentration will increase by one of two mechanisms: sodium retention in patients who are hypovolemic, or initial retention of the sodium followed by the excretion of water in patients with SIADH. In the latter disorder, volume regulation is intact and the administered sodium will be excreted in the urine through associated volume expansion. The water loss induced by excretion of the extra sodium is responsible for the steady-state elevation in the plasma sodium concentration.

HYPONATREMIA IN ELDERLY PATIENTS: A SPECIAL SITUATION

Older people may be predisposed to hyponatremia because of medications or diseases that cause or are associated with low concentrations of serum sodium.[22] Another controversial proposed cause is an enhanced vasopressin response to hyperosmolarity that may occur with increasing age.[22]

Congestive heart failure is an important cause of hyponatremia in elderly people. Although the total extracellular fluid volume is increased in patients with heart failure, they are functionally hypovolemic because of low cardiac output. The decrease in tissue perfusion stimulates the release of ADH. This process is directly related to the severity of the hemodynamic impairment. As a result, hyponatremia in congestive heart failure is a marker of a poor prognosis. Symptoms of hyponatremia occur primarily with acute reductions in the plasma sodium concentration and are vague and unreliable in elderly people. Symptoms that may be seen include lethargy, confusion, agitation, weakness, and anorexia.

An important aspect of the evaluation of elderly patients who have low plasma osmolality is an accurate assessment of their volume status—a challenging task in these patients.

Our patient was treated with intravenous isotonic sodium chloride solution, and her serum sodium level was corrected to 120 mmol/L after the first 24 hours. Her neurologic state improved gradually over the next 3 days. A regimen of lisinopril, 10 mg a day, was started for blood pressure control, and the patient was discharged to home in good condition.

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